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TITLE: Magnetic stimulation and epilepsy

PRINCIPAL INVESTIGATOR: Ching-Yi Lin PhD

CONTRACTING ORGANIZATION: Cleveland Clinic Foundation
Cleveland, OH 44195

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Fort Detrick, Maryland 21702-5012

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. Cleveland Clinic Foundation
Cleveland, OH 44195

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14. ABSTRACT
During previous 22 months of project, we have reached several milestones according to the time frame that has been proposed in the grant. For the Specific Aim 3, the penicillin-induced seizure animal model has been generated by acute focal intracortical injection of penicillin in the motor cortex of rats. The fects of transcranial magnetic stimulation (TMS) on penicillin-induced seizure have been investigated using behavioral recording and electroencephalographic

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Annual Progress Report

For the period of September 15, 2012 through September 30, 2013

I. BASIC INFORMATION

SUBJECT: Magnetic stimulation and epilepsy

AWARD #: W81XWH-11-1-0707

CCF IACUC#: 2010-0415 (expires March 6, 2014)

SPONSOR: Department of Defense (DoD) Telemedicine and Advanced Technology Research Center

PRINCIPAL INVESTIGATOR: Ching-Yi Lin PhD

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REPORT DATE : October 14, 2013

II. STUDY PROGRESS

A. Summary: Study Progress in Relation to Investigational Plan

During previous 22 months of project, we have reached several milestones according to the time frame that has been proposed in the grant. For the Specific Aim 3, the penicillin-induced seizure animal model has been generated by acute focal intracortical injection of penicillin in the motor cortex of rats. The effects of transcranial magnetic stimulation (TMS) on penicillin-induced seizure have been investigated using behavioral recording and electroencephalographic (EEG) recording. The results (**Figures 1~7**) obtained have been submitted to *Epilepsia*.

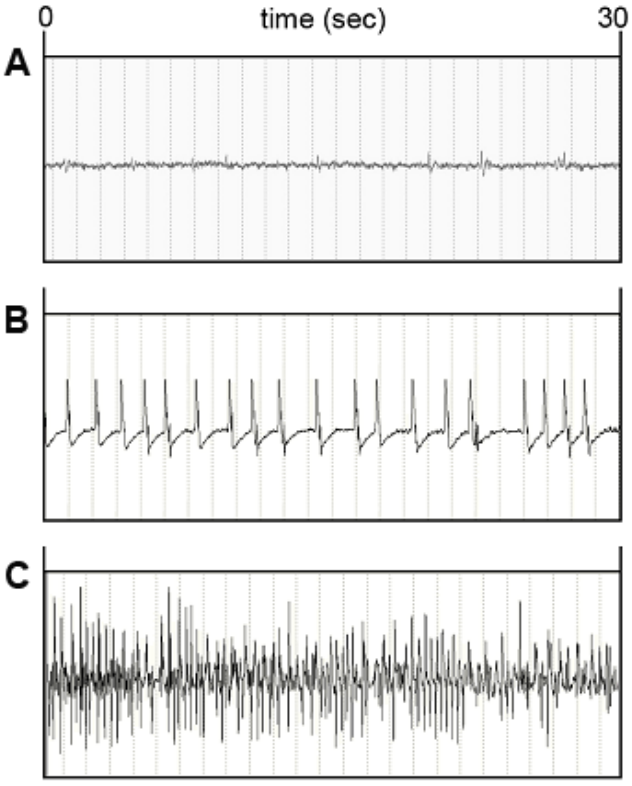


Figure 1. *Representative EEG segments with intracortical injection of penicillin. All EEG segments were taken at 30 μV sensitivity and 1.6-70 Hz frequency range (**A**, **B**, **C**). 3 EEG segments that depict EEG during penicillin injection (**A**), myoclonic jerks (**B**), and GTC seizures (**C**), respectively.*

All rats developed a focal epileptic status after penicillin injection in the frontal cortex as compared to baseline EEG activity (Fig. 1A), detected by both real-time EEG and video recording. The penicillin-induced EEG seizures, characterized by a combination of myoclonic jerks (Fig. 1B) and GTC seizures (Fig. 1C) within 30 minutes post-injection, were tightly associated with contralateral forelimb clonic movement captured by live video recording.

A Density Spectral Array (DSA) trend graph (Nihon Kohden EEG recording software) was first used to chart the frequency components of EEG and their respective power over the entire recording session. A 30-minute DSA segment of an experimental group's trend graphs (a-h in Fig. 2B) was selected to illustrate the general EEG activity at all major time-points of interest identified in the timeline (Fig. 2A). Animals with penicillin seizure induction (animal groups 3-6) exhibited a full response to the drug approximately 30 minutes post-penicillin injection (30 min-PI; b). DSA trend graphs (c-h) were all periodically taken at time-points post-TMS treatment. The non-seizure induction groups (groups 1, 2) maintained an EEG frequency component of less than 8 Hz at all time-points, consistent with the seizure-free baseline of all animal groups in (a). Animals with seizure induction but without TMS treatment (group 3) displayed full, epileptic seizure responses from 30min-PI (b) up until the 5-hour recording mark (b-f), with signs of diminishing seizures 8 hours after TMS treatment (g). Animals treated with high frequency TMS at 10 pps (group 6) displayed

DSA trendgraphs identical to the non-TMS treated group (group 3). Animals treated with TMS at the lower frequencies of 1 (group 4) or 5 (group 5) pps showed signs of seizure suppression as early as 10 minutes post-TMS stimulation (10 min-PS; c) and gradually descended until stable conditions were achieved by the 24-hour mark (h). Eight hours after TMS stimulation (g), the seizure-induced groups exhibited varying degrees of EEG activity reduction.

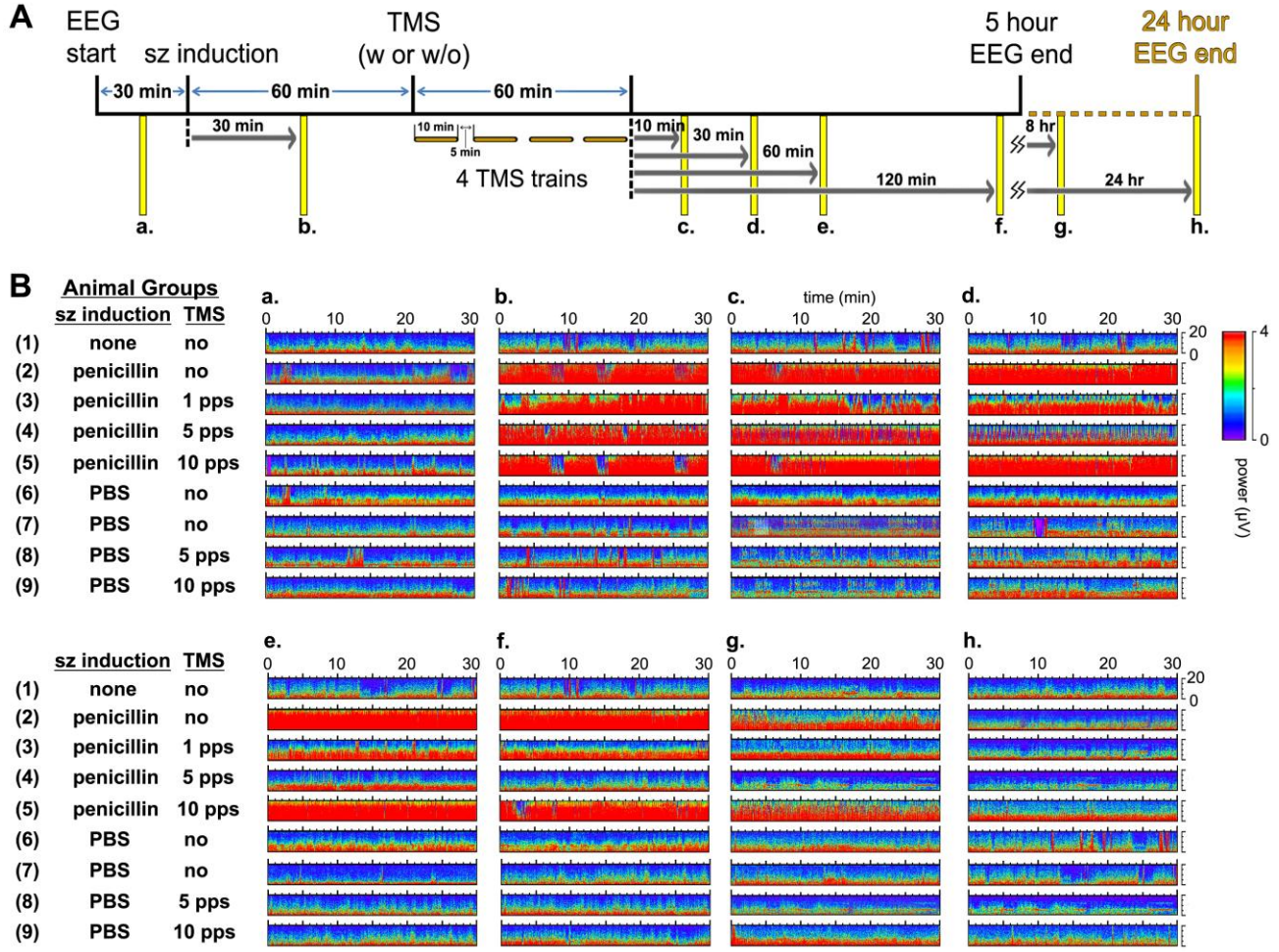


Figure 2. *The effects of TMS on penicillin-induced seizures over time were characterized using DSA trendgraphs. (A) Timeline of the experimental events and time-points of interest (marked "a-h") during EEG recording. (B) A series of DSA trendgraphs, which displayed the frequency components of EEG (y-axis) and their respective amplitudes (color bar) as a function of time. Red regions found in the high frequency range correlated to potent seizure (sz) activity, whereas EEG activity found at low frequencies indicated stable, normal conditions. Red and purple represented the highest and lowest amplitudes, respectively. TMS was administered at three different frequencies: 1, 5 and 10 pps. As shown, all groups' respective DSA trendgraphs were layered against one another at varying time-points along the EEG recording including (a) baseline (pre-penicillin injection), (b) 30-min post-penicillin injection (30min-PI), (c) 10-min post-TMS stimulation (10min-PS), (d) 30min-PS, (e) 60min-PS, (f) 120min-PS, (g) 8 hours post-penicillin injection (8h-PI), and (h) 24h-PI. Experimental groups included: (1) none/no TMS, (2) penicillin/no TMS, (3) penicillin/1 pps TMS, (4) penicillin/5 pps TMS, (5) penicillin/10 pps TMS, (6) PBS/no TMS, (7) PBS/1 pps TMS, (8) PBS/5 pps TMS, and (9) PBS/10 pps TMS.*

Fig. 3 shows the frequency components measured and trended during each of the DSA time-points, with the 20 Hz maximum defined as 100% and used as a reference point (Fig. 3A). A linear trend line was calculated against the frequency component values to approximate the rate of seizure deterioration (Fig. 3B). The non-TMS treated group acted as a baseline regression rate from 20 Hz to stable, seizure-free conditions. The 1 pps TMS-treated group was calculated to regress to stable conditions 55% faster, and the 5 pps TMS-treated group 78% faster.

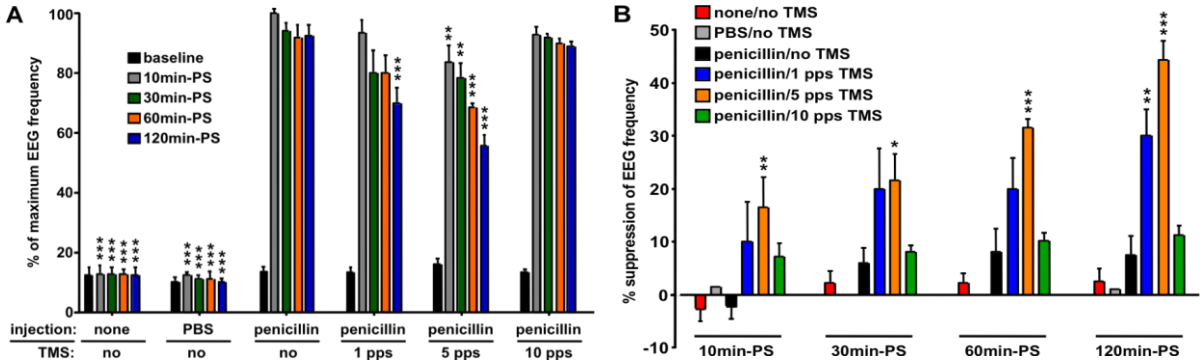


Figure 3. *Maximum frequency relationships in EEG activity among the groups at various time points. After an electrode/cannula implantation, rats underwent an EEG recording session that included both administration of penicillin as well as TMS treatment. Frequency and the amplitudes at each frequency measured over time were reliable guidelines to depict overall EEG activity, such that a combination of high amplitudes and frequencies indicated potent seizure activity. Maximum frequency/amplitude values were recorded at various time points in the EEG and labeled as 10min-PS. (**A**) A total % of maximum EEG frequency, using the DSA trendgraph maximum value indicating full response to the penicillin-induced seizures (as data has shown in 30min-PI). (**B**) A suppression in % of EEG frequency using each group's own 30min-PI frequency as a reference value.*

Fig. 4 charts the total number of spikes counted within each 5-minute segment at each time-point of interest. The 1 pps TMS-treated group was found to recede in spike count 83% faster and the 5 pps TMS-treated group 94% faster as compared to the no TMS-treated group. The 10 pps TMS-treated group, on the other hand, experienced a 26% slower rate in spike count reduction as compared to the no TMS-treated group. Regarding the 24-hour chart (Fig. 4B), the 5 pps TMS-treated group hit a zero spike count (recorded at the 7h-PI) nearly 3 hours prior to both the 1 pps TMS-treated group and the no TMS-treated groups (recorded at the 10h-PI).

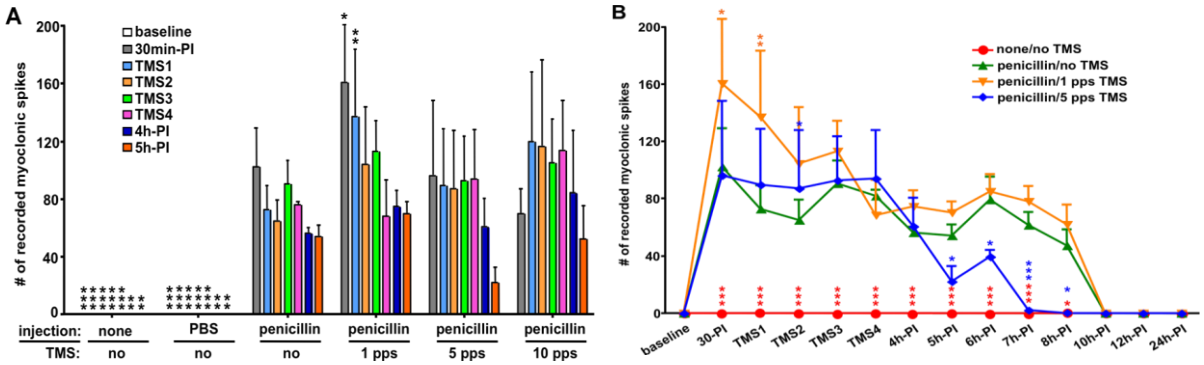
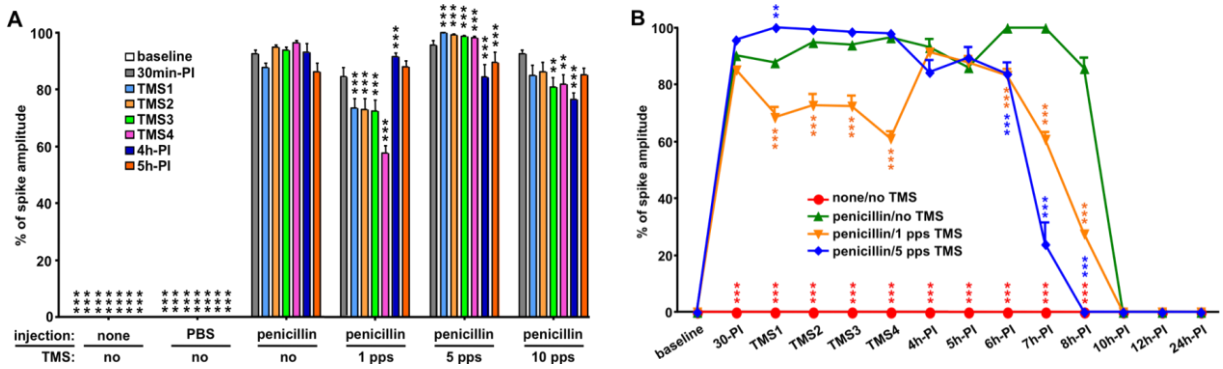


Figure 4. *Myoclonic spike counts during EEG segments at various time-points. At designated time-points over the course of the recording, all occurrences of myoclonic EEG seizure spikes coordinated with*

*behavioral myoclonic jerks were counted over the course of the 5-minute segments at each of the time-points. (**A**) Short-term timeframe graph (5 hours) focused on the immediate effects of the TMS session in all animal groups. (**B**) Long-term timeframe graph (24 hours) focused on spike count trends over the lifetime of the penicillin-induced seizures.*

At the 30-PI time point, all seizure induction groups experienced full responses to the penicillin-induced seizures and consistently displayed amplitudes of around 80-100%. After TMS treatment, seizure induction groups began to differentiate. In the non-TMS treated group and the 5 pps TMS group, amplitudes were wholly uninfluenced by the TMS and plateaued at their 30-PI value. The 10 pps TMS group displayed a slight suppression of amplitude (approximately 10% over the course of the treatment). The lowest frequency of the TMS treatment groups (1 pps), however, showed an immediate ~30% amplitude reduction, with up to a ~40% reduction after the 4th TMS train (TMS4). By post-TMS treatment, beginning at the 4h time-point (4h-PI equal to 1.5 hours after TMS4), all signs of amplitude reduction were reverted to an amplitude value akin to the full response at 30-PI (Fig. 5B).

Figure 5. *Myoclonic spike amplitudes during EEG segments at various time-points. At designated time-points over the course of the recording, amplitude values were recorded on all myoclonic spikes coordinated in both EEG spikes and video behavior. Due to experimental equipment limitations, the maximum amplitude value clipped at 675 μV, and was thus used as a 100% reference. All recorded amplitude values were then converted to a percentage-based system for easier trend interpretation. (**A**)*



*Short-term timeframe graph (5 hours) focused on the immediate effects of the TMS session in all animal groups. (**B**) Long-term timeframe graph (24 hours) focused on amplitude trends over the lifetime of the penicillin-induced seizures.*

All animal groups, with the exception of the 10 pps TMS-treated group, experienced a maximum in spike frequency at the 30 min-PI time-point (Fig.6). From there, spike frequency declined at varied rates until seizures fully subsided. In contrast, the 10 pps TMS-treated group increased 50% in spike frequency after its first session of TMS (TMS1) and maintained that frequency for the remainder of the 5-hour recording (Fig.6A). Linear trend lines were applied to help approximate the spike frequency regression rate amongst animal groups, using the non-treated group as the baseline for an untreated regression rate. A higher rate of spike frequency regression implies less myoclonic jerks per second experienced between subsequent time-points. In comparison to the non-treated group, the 1 pps TMS treatment group displayed an approximate 40% higher rate of regression in spike frequency. In comparison, the 5 pps TMS treated group showed a 26% increase in regression rate (Fig.6B). Although restricted to the 5-hr recording time frame, the 10 pps TMS treatment group displayed an increasing trend in frequency at about 48% the rate of baseline, contrary to the steadily diminishing values of the other TMS-treated groups (Fig. 6A).

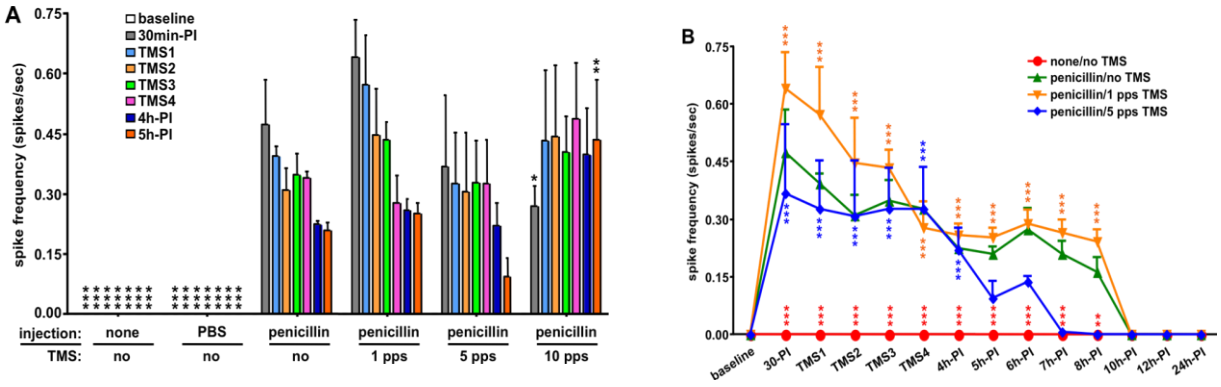


Figure 6. *Myoclonic spike frequency during EEG segments at various time-points. At designated time-points over the course of the recording, time in between all documented myoclonic spikes, coordinated in both EEG spikes and video behavior, were recorded. Interval values were then averaged amongst an EEG segment timeframe and converted to a spikes-per-second frequency. (**A**) Short-term timeframe graph (5 hours) focused on the immediate effects of the TMS session in all animal groups. (**B**) Long-term timeframe graph (24 hours) focused on frequency trends over the lifetime of the penicillin-induced seizures.*

As shown in Fig. 7, the 10 pps TMS-treated group experienced relatively consistent levels of GTC seizures up until the 4 hour time-point (4h-PI), spending between 15-25% of their time segments in GTC seizures. At 5h-PI, however, the 10 pps TMS-treated group spent beyond 30% of time in GTC seizures (Fig. 7A). In contrast, the maximum percentage of the time spent in GTC seizures by the rest of the seizure induction groups during the TMS session time-points (TMS 1, 2, 3, 4) was 30% for no TMS-treated, 20% for 1 pps TMS-treated and 18% for 5 pps TMS-treated groups, which was sharply reduced to zero by 6h-PI. Looking closer at the 5-hour time-point (5h-PI), during their decline toward zero, the no TMS-treated group recorded 10% of time spent in GTC seizures, the 1 pps TMS-treated group recorded 5.6%, and the 5 pps TMS-treated group recorded 4%, as compared to the 10 pps TMS-treated group (32%). Regarding the 24-hour timeframe chart (Fig. 7B), all seizure induction groups experienced GTC seizures during the 30min-PI time-point. Immediately afterwards, however, each groups' recorded time spent in GTC seizures varied significantly during the TMS treatment session. On average, the no TMS-treated group spent 33% of an EEG segment in GTC seizures. On the other hand, the 1 pps TMS-treated group averaged 21% of its time in GTC seizures, compared to the 5 pps TMS-treated group average of 18% in GTC seizures. Unlike the 1 pps TMS-treated group's suppressive effects on spike amplitude that immediately reverted to normal after the TMS session (TMS 1, 2, 3, 4), both of the lower TMS-treated groups' (1 and 5 pps) suppressive effects on the volume of GTC seizures carried over after the treatment session. Particularly, the carry-over effects resulted in up to a 60% reduction in GTC seizures in the 5 pps TMS-treated group during 5h-PI.

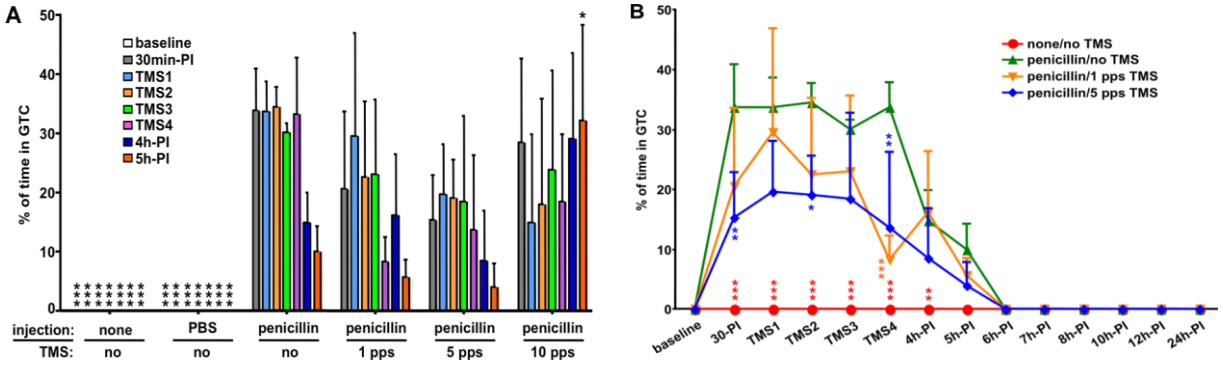


Figure 7. *Percentage of time spent in GTC seizures during EEG segments at various time-points. At designated time-points over the course of the recording, all instances of GTC seizures were recorded over the course of each time-point's 5-minute EEG segment. To convert to a percentage-based system, the total duration of time spent in GTC seizures was then divided by the length of the EEG segment. (**A**) Short-term timeframe graph (5 hours) focused on the immediate effects of the TMS session in all animal groups. (**B**) Long-term timeframe graph (24 hours) focused on percentage of time spent in GTC seizures over the lifetime of the penicillin-induced seizures.*

For the Specific Aim 1 and 2, we investigate if magnetic stimulation (MS) influences the neurite outgrowth by neurons. While the experiments are still ongoing, we do see the effects of MS on neurite outgrowth, and these effects are depend on the frequency of MS applied.

Neuroscreen-1 cells, subclones of PC12, known for rapid growth and ideal sensitivity to neurotrophic growth factors were chosen for our experiments. Neuroscreen-1 cells exposed to MS expressed longer neurites, although to different degrees depending on the frequency (1, 5 or 10 pps) of MS applied. Bars show groups for five individual experiments. As shown, MS applied at 10 pps increased the length of neuritesas compared to control group (CON) no matter machine output (MO) was set at 30 or 40 %. However, such increases in neurite length did not happen as compared to control group when the MS was set at relative lower frequency, both 1 and 5 pps.

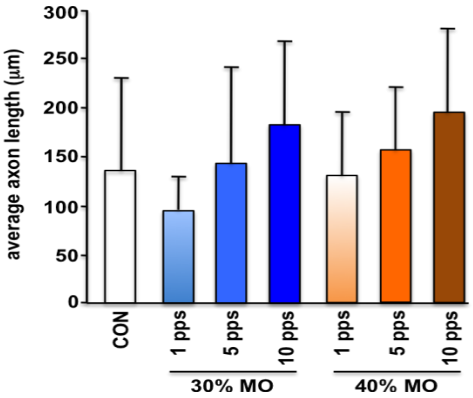


Figure 8. *Neurite outgrowth was regulated by MS. Neuroscreen-1 cells were added to a collagen-coated coverslip. MS at 1, 5, or 10 pps was applied beginning on the second day, twice a day for additional 3 days. The NS-1 cells were then fixed and stained for both beta III tubulin and HCS CellMask Red. Images were captured using the QCapture Pro software, and neurite lengths measured with the program ImageJ. The average neurite length was examined for every treatment condition.*

B. Investigators/Investigational Sites

The study is being conducted at only one site – Cleveland Clinic Foundation. There are no plans to add another site.

Investigational Site	Investigators
Cleveland Clinic Foundation 9500 Euclid Avenue, Cleveland, OH 44195	Ching-Yi Lin PhD

C. Number of Subjects / Animals

111 rats were used for the study.

D. Summary of Anticipated and Unanticipated Adverse Effects
N/A

E. Investigational Devices
N/A

F. Deviations from Investigational Plan

No deviations from the investigational plan.

III. RISK ANALYSIS

A. New Adverse Information and New Risk Analysis

No new risks have been identified that would require a new risk analysis.

B. Publications and Presentations
Li, K., Y.-S. Lee, L. Franic, J. Gonzalez-Martinez, V. W. Lin, I. Najm, **C.-Y. Lin**. The anti-convulsive effects of Transcranial Magnetic Stimulation (TMS) on penicillin-induced seizures. 2012, LRI retreat, Ohio (Corporate College East), USA.

Li, K., Y.-S. Lee, L. Franic, J. Gonzalez-Martinez, V. W. Lin, I. Najm, **C.-Y. Lin**. The anti-convulsive effects of Transcranial Magnetic Stimulation (TMS) on penicillin-induced seizures. 2012, Cleveland Clinic Research Day, Ohio, USA.

Lee, Y.-S., K. Li, L. Franic, J. Gonzalez-Martinez, V. W. Lin, I. Najm, *** C.-Y. Lin**. 2013. Frequency-Dependent Effects of Transcranial Magnetic Stimulation on Penicillin-Induced Seizures in Rats. *Society for Neuroscience (submitted)*.

Lee, Y.-S., K. Li, L. Franic, J. Gonzalez-Martinez, V. W. Lin, I. Najm, *** C.-Y. Lin**. 2013. Frequency-Dependent Effects of Transcranial Magnetic Stimulation on Penicillin-Induced Seizures in Rats. *Epilepsia (submitted)*. * corresponding author.

IV. OTHER CHANGES

N/A

V. FUTURE PLANS

The additional year (no-cost extension) will be used to conduct the experimental progress to investigate (i) the effects of MS on the level of BDNF (Aim 1; 50% of initial work proposed is remaining); (ii) the roles of BDNF on the MS regulation of neurite outgrowth (Aim 2a & 2b; 20% of initial work remaining); (iii) if MS also works to enhance neurite outgrowth when NS-1 cells were grown on the growth-inhibitory substrate (Aim 1c; 20% of initial work remaining); (iv) if regulation of BDNF level by TMS accounts for TMS suppression of seizure (Aim 3b; 60% of initial work remaining).

Annual Progress Report

For the period of September 15, 2012 through September 30, 2013

I. BASIC INFORMATION

AWARD NUMBER: W81XWH-11-10707

IRB NUMBER: 11-823 (expiration date: 9/8/2014)

STUDY NAME: Directing Neuroplasticity to Improve Rehabilitative Outcomes of the Upper Limb in Incomplete Quadriplegia

SPONSOR: Department of Defense (DoD) Telemedicine and Advance Technology Research Center

PI: Ela Plow PhD PT
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CLEVELAND, OHIO 44106

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REPORT DATE : October 14, 2013

II. STUDY PROGRESS

A. Summary: Study Progress in Relation to Investigational Plan

The long-term objective of our study is to maximize the rehabilitative potential in spinal cord injury (SCI). We are addressing this goal by harnessing the maximal potential available for neuroplasticity in patients with SCI. SCI is an important cause of serious, long-term disability in young adults. Upper limb dysfunction is one of the most prevalent and debilitating impairments. Although various therapuetic programs have been employed to mitigate functional impairments of the arm and hand, effects are weak and invariable. *Limited succcess of rehabilitation is speculated to be associated with maladaptive changes in the brain*; for instance, maps in the motor cortex (M1) devoted to intact parts of limbs expand at the expense of maps devoted to the more affected parts, limiting effects of training involving the impaired segments. Recovery can be served by adaptive changes of maps in the M1 that potentially improve descending motor output to affected limbs.

Our ***objective*** is to directly modulate adaptive plasticity in M1 and CST using brain stimulation to enhance function of the upper limb in iSCI. Our ***central hypothesis*** is that a noninvasive form of brain stimulation, called transcranial direct current stimulation (tDCS), when directed to representations of the affected upper limb in M1, during rehabilitation, will generate synergistic functional advantage. Adaptive functional and structural plasticty, in M1 and CST, will underlie such advantage and will be demonstratable using noninvasive Transcranial Magnetic Stimulation (TMS) and Diffusion Tensor Imaging (DTI) in patients.

B. Investigators/Investigational Sites

The study is being conducted at only one site – Cleveland Clinic Foundation. There are no plans to add another site.

Investigational Site	Investigators
Cleveland Clinic Foundation 9500 Euclid Avenue, Cleveland, OH 44195	Ela Plow PhD PT Frederick Frost MD Ken Sakaie PhD

C. Number of Subjects

Two SCI subject and three control subjects have been enrolled.

Ethnic/Racial Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	0	0	0
American Indian/ Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
African-American	0	0	0
White	0	5	5
Ethnic/Racial Category Total	0	5	5

D. Investigational Devices
N/A

E. Summary of Results

The aims of the clinical research trial remain as originally funded. We have, however, modified treatment program, so aims 1 and 2 are modified now slightly. With communication from potential candidates with spinal cord injury and physicians in the area treating these patients, we have found that enrolling in a 5-week control period and a 5-week intervention phase would be impractical for most patients to adhere to as travelling to and from clinic every day is logistically difficult for patients for 5 continuous weeks. Thus, we have, with approval from our Institutional Review Board and the Human Research Protection Office, reduced the control phase and treatment phases to 2 weeks each.

Findings from age-matched control subjects has provided us with

- Norms for performance-based tests of motor skill (speed, accuracy, quality of movement)
- Feasibility of acquiring high-quality imaging data and using advanced analysis
- TMS-based cortical/corticospinal excitability and size of representations devoted to various muscles.
- Analysis of DTI is underway, but preliminary exploration indicates that distinguishing between corticospinal tracts to various representations of muscles of hand is feasible.

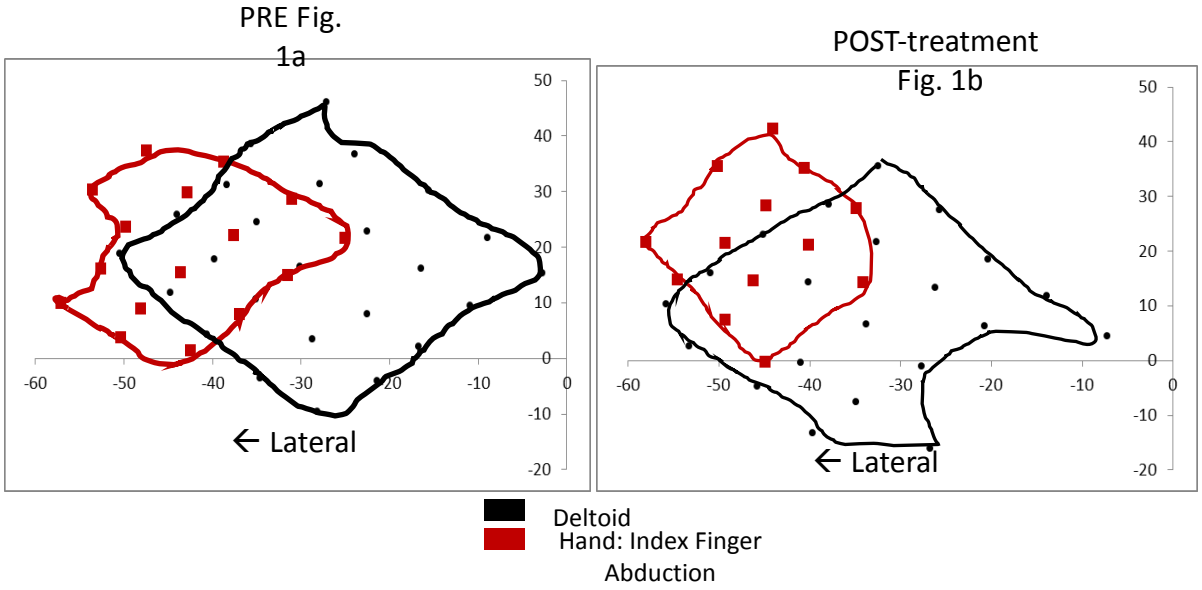
Towards our primary objective, we have found that in a 52 year old male with spinal cord injury, who recently completed the study, we witnessed remarkable recovery with only 2 hrs of rehabilitation delivered daily for 2 weeks when it was combined with brain stimulation. These improvements were greater than changes noted in the control phase of study. Overall, patient's function on grasp, grip and gross upper limb movements improved more than his dexterity (Table 1); this was the intent of therapy since he was relatively weaker proximally than distally. The improvement in function was associated with improvement in strength of key proximal and distal muscles (Table 2).

Table 1: Functonal tests	*Percent improvement*
Grasp	50%
Grip	50%
Proximal Shoulder Movements	50%
Dexterity on Nine-Hole Peg test	9%

Table. 2: Muscle Strength Test	*Pre-Treatment*	*Post-Treatment*
Deltoid	2-	2+
Biceps	2-	2+
Triceps	3+	4
Wrist Flexors	2+	3+
Wrist Extensor	2+	3+
Supinator	2-	3
Index Finger Abduction	2+	3
Thumb Abduction and Opposition	2+	4

Evaluation with TMS mapping shows maps in the brain devoted to deltoid (more affected muscle) and hand (less affected muscle) reorganize from pre- (Fig. 1a) to post-treatment (Fig. 1b). Maps devoted to more affected deltoid muscle, which was trained extensively, enlarge and show a shift

towards map of the less-affected hand muscle (index finger abductor). Maps of deltoid muscle and hand muscle overlap more following training. Therefore, in line with aim 1 of the study, we have case findings that indicate that patient with SCI receiving brain stimulation during rehabilitation shows greater benefit in upper limb function than in control phase (Tables 1 and 2); these improvements are greater for more-affected muscles (deltoid and elbow flexors) that were emphasized in training. In line with aim 2, it appears that these functional improvements in the more affected muscles (deltoid) may be explained by reorganization of their maps in the brain, which tend to enlarge and occupy M1 territory devoted to the less-affected muscle (index finger abductor) (Fig. 1a and b).



F. Summary of Anticipated and Unanticipated Adverse Effects

N/A

G. Deviations from Investigational Plan

No deviations from the investigational plan.

III. RISK ANALYSIS

A. New Adverse Information and New Risk Analysis

No new risks have been identified that would require a new risk analysis. The study is now registered as a pilot clinical trial. Use of tDCS, TMS and structural and functional MR imaging poses some risk, but strict adherence to inclusion-exclusion criteria, and protection against risks in conjunction with Clinical and Translational Science Association's Clinical Research Unit assistance has helped attenuate any safety threats.

B. Publications and Presentations

Publications directly resulting from this award in the in the 1st year: None

Publications in the general area of PI's research in brain stimulation and MRI in 1st year of grant:

a. Plow EB, Obretenova SN, Halko MA, Kenkel S, Jackson ML, Pascual-Leone A, Merabet LB (2011) Combining Visual Rehabilitative Training and Noninvasive Brain Stimulation to Enhance Visual Function in Patients with Hemianopia: A Comparative Case Study. *Physical Medicine and Rehabilitation* 3(9):825-835. *PMID: 21944300*

b. Plow EB, Obretenova SN, Fregni F, Pascual-Leone A, Merabet LB (2012) Comparison of visual field training for hemianopia with active versus sham transcranial direct cortical stimulation. *Neurorehabilitation and Neural Repair (Epub) PMID: 22291042*

c. Plow EB, Obretenova SN, Merabet LB (2012) Temporal Profile of Functional Visual Rehabilitative Outcomes Modulated by Transcranial Direct Current Stimulation (tDCS). *Neuromodulation: Issue on Technology at Neural Interface (Epub) PMID: 22376226*

d. Plow EB, Pascual-Leone A, Machado A (2012) Brain Stimulation in the Treatment of Chronic Neuropathic and Non-Cancerous Pain. *Journal of Pain (Epub) PMID: 22484179*

e. Plow EB and Carey JR (2012). Pilot fMRI Investigation of Representational Plasticity associated with Motor Skill Learning and its Functional Consequences. *Brain Imaging and Behavior (Epub) PMID: 22454141*

f. Machado A, Baker K, **Plow EB**, Malone D (2012). *Cerebral stimulation for the affective component of neuropathic pain.* Neuromodulation: Technology at the Neural Interface (*in press*)

IV. OTHER CHANGES

N/A

V. FUTURE PLANS

The study takes place at the Cleveland Clinic. Since Cleveland Clinic is not the primary site for clinical treatment for patients with SCI, recruitment is challenging. Therefore, we have established links with hospitals in the Cleveland area that treat SCI patients, including MetroHealth and Veterans Affairs hospital in Cleveland. To further facilitate recruitment, we requested and received HRPO approval to use provider lists from Cleveland Clinic as a method to review potential patients. Since this approval was received on 7-30-2012, our recruitment efforts have expanded. Five interested patients are waiting to be followed up with. We have further expanded recruitment efforts to include contact of support groups, community initiatives in the area of Cleveland and reaching out to rehabilitation facilities in farther parts of Ohio and Pennsylvania states.

Annual Progress Report
For the period of September 15, 2012 through September 30, 2013

I. BASIC INFORMATION

SUBJECT: Expiratory Muscle Conditioning Using Functional Magnetic Stimulation (FMS) for Patients with Multiple Sclerosis

AWARD #: W81XWH-11-1-0707

CCF IRB#: 11-780 (expiration date: 9/29/2014)

SPONSOR: Department of Defense (DoD) Telemedicine and Advanced Technology Research Center

PRINCIPAL INVESTIGATOR: Vernon Lin MD PhD

CONTACT PERSON: Vernon Lin MD PhD

E-MAIL: linv@ccf.org

REPORT DATE: 10/14/2013

II. STUDY PROGRESS

A. Summary: Study Progress in Relation to Investigational Plan

The research study was reviewed and fully approved by Cleveland Clinic IRB. The expiration date is 9/29/2014. Xiaoming Zhang, PhD was hired in September 2012 as a co-investigator to manage the day-to-day activities of the project, participate in subject screening, data collection and analysis, manuscript and report preparation and dissemination of study results.

The MagPro R30 magnetic stimulator in July 2012 and the investigators completed training with the system. The team started to screen subjects with multiple sclerosis (MS) in September 2012. Inclusion criteria for this study are subjects with clinically defined MS whose baseline maximal expiratory pressure (MEP) values are between 50% and 70% of predicted. The medical records of approximately 200 MS patients were screened. The study has so far enrolled and completed data collection for 2 subjects.

B. Investigators/Investigational Sites

The study is being conducted at only one site – Cleveland Clinic Foundation. There are no plans to add another site.

Investigational Site	Investigators
Cleveland Clinic Foundation 9500 Euclid Avenue, Cleveland, OH 44195	Vernon Lin MD PhD Francois Bethoux MD Vinoth Ranganathan MSE MBA Xiaoming Zhang PhD Ela Plow PhD PT

All subject records and documentation will be kept in the FMS Laboratory at Cleveland Clinic Foundation.

C. Number of Subjects

Two subjects have completed the protocol. Approximately 25 charts are screened each month to identify potential subjects.

Ethnic/Racial Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	0	0	0
American Indian/ Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
African-American	0	0	0
White	1	1	2
Ethnic/Racial Category Total	1	1	2

D. Investigational Devices
N/A

E. Summary of Results

Two MS patients were recruited for the 6-week FMS conditioning protocol. FMS of spinal cord nerves resulted in significant respiratory pressures (maximum expiratory pressure, MEP), flow (peak expiratory plow, PEF), and volumes (expiratory reserve volume, ERV). Table below shows the improvements of MEP before, during, and after FMS conditioning protocol. The improvements peaked around 4 weeks in to FMS intervention and then plateaued or slightly declined. The pre-FMS values of MEP were 76 cmH_2O and 62 cmH_2O for these two patients. The value increased to 83 cmH_2O and 72 cmH_2O after 4-week FMS training. These values correspond to a 9.2% and 16.1% increase compared to the baseline MEP for the two subjects. Similar increases were also observed in PEF and ERV. The improvements seen in respiratory function returned back to baseline two weeks after FMS conditioning protocol was stopped.

Patient #1	**MEP (cmH_2O)**	**PEF (L/sec)**	**ERV (liter)**
Baseline	76	6.01	0.53
2 wk	84	6.16	0.59
4 wk	83	7.65	0.56
6 wk	80	7.23	0.61
Follow-up	79	6.49	0.58
Patient #2	**MEP (cmH_2O)**	**PEF (L/sec)**	**ERV (liter)**
Baseline	62	3.7	0.72
2 wk	70	3.66	0.81
4 wk	72	4.36	0.80
6 wk	71	4.04	0.78
Follow-up	70.5	3.92	0.68

F. Summary of Anticipated and Unanticipated Adverse Effects

N/A

G. Deviations from Investigational Plan

No deviations from the investigational plan.

III. RISK ANALYSIS

A. New Adverse Information and New Risk Analysis

No new risks have been identified that would require a new risk analysis.

B. Publications and Presentations

N/A

IV. OTHER CHANGES

N/A

V. FUTURE PLANS

The protocol has received a one year no-cost extension. The study team will continue to screen MS subjects for the study. Investigators will recruit 6 more subjects as specified in the study protocol. The enrollment rate has been very low because patients live outside of Cleveland or do not have transportation available to visit our research lab 5 days/week for 6-weeks. An eligible subject has expressed interest in the study and will be enrolled shortly. Study team expects to enroll the remaining study subjects in the next 8-10 months and complete the protocol.

Annual Progress Report
For the period of September 15, 2012 through September 30, 2013

I. BASIC INFORMATION

AWARD NUMBER: Proposal log number 10176004, Award Number W81XWH-11-10707

IRB NUMBER: 11-182 (expiration date: 04/07/2014)

STUDY NAME: A trial to compare the efficacy of Functional Magnetic Stimulation in enhancing GI motility in patients with constipation.

SPONSOR: Department of Defense (DoD) Telemedicine and Advance Technology Research Center

INDICATIONS FOR USE: Slow transit constipation

PI: Massarat Zutshi
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REPORT DATE : October 14, 2013

II. STUDY PROGRESS

A. Summary: Study Progress in Relation to Investigational Plan

The study will evaluate the effects of functional magnetic stimulation (FMS) on colonic transit in non neurological constipated patients. Inclusion criteria for this study are subjects with clinically defined non-neurological constipation. Chronic functional constipation will be defined by the Rome II criteria and slow colonic transit will be documented by a Smart Pill whch is wireless motility pill study. Eligible subjects will have a colonic transit time that is significantly longer than healthy subjects (>60hrs). The timing of treatment is a 5-week conditioning protocol. Sixteen patients are to be randomized to receive either the treatment or sham with a crossover design. Patients will be evaluated with the Smart Pill after receiving treatment. The site received IRB approval of the amendment (Protocol Version 3) on August 7, 2012 and approval from HRPO on 8/23/2012.

During the current reporting period, the study team was unable to recruit any subjects due to the following factors:

1. Patients do not want to be randomized as they need to set aside 10 weeks for treatment if they receive sham treatment. This is not feasible for working patients.
2. Smart Pill procedure prior to treatment was not budgeted for the study. It was to be billed to the patients insurance as it is considered standard of care. However, most insurance will not pay for it as they still continue to consider using SmartPill as investigational. As a result, most patients under going SmartPill procedure have to pay more than $2000 as out of pocket expense which most patients cannot afford. Patients who pay this huge out-of pocket expense do not wish to be part of a study where they could be receiving sham treatment.
3. The enrollment rate has been difficult because most of the eligible patients live outside of Cleveland or do not have reliable transportation available to visit our research lab 5 days/week for 6-weeks.

Due to these issues, it has been very difficult to enroll subjects for this pilot study. The PI has been working with the patient's insurance payors on a case-by-case basis to get insurance coverage (similar to patients receiving standard of care treatment). The PI is also working with HRPO to modify the protocol (remove the sham treatment) and to cover the cost of the Smart Pill.

B. Investigators/Investigational Sites

The study is being conducted at only one site – Cleveland Clinic Foundation. There are no plans to add another site. No changes were made to the study team during this reporting period.

Investigational Site	Investigators
Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Oh 44195	Massarat Zutshi,MD Xiaoming Zhang PhD Tracy Hull MD Brooke Gurland MD

All regulatory documentations are kept at the Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland Oh 44195.

C. Number of Subjects

The medical records of approximately 9 chronic constipation patients were screened.

4 patients qualified
2 patients insurance refused to cover the Smart Pill procedure
2 patients are ready for enrollment if Smart pill is covered and randomization clause removed.

As of date, no patients have been enrolled or participated in the study.

D. Investigational Devices

N/A

E. Summary of Results

There are no results.

F. Summary of Anticipated and Unanticipated Adverse Effects

III. RISK ANALYSIS

A. New Adverse Information and New Risk Analysis

None

B. Publications and Presentations

None

IV. OTHER CHANGES

None

V. FUTURE PLANS

The PI will request DOD HRPO and Cleveland Clinic IRB to remove the sham treatment group. The PI will also request approval to cover the costs of the SmartPill using study funds (no additional funds requested) as the cost has been identified as a major barrier to enroll eligible subjects.